Cholera in the United States

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ACIP Meeting
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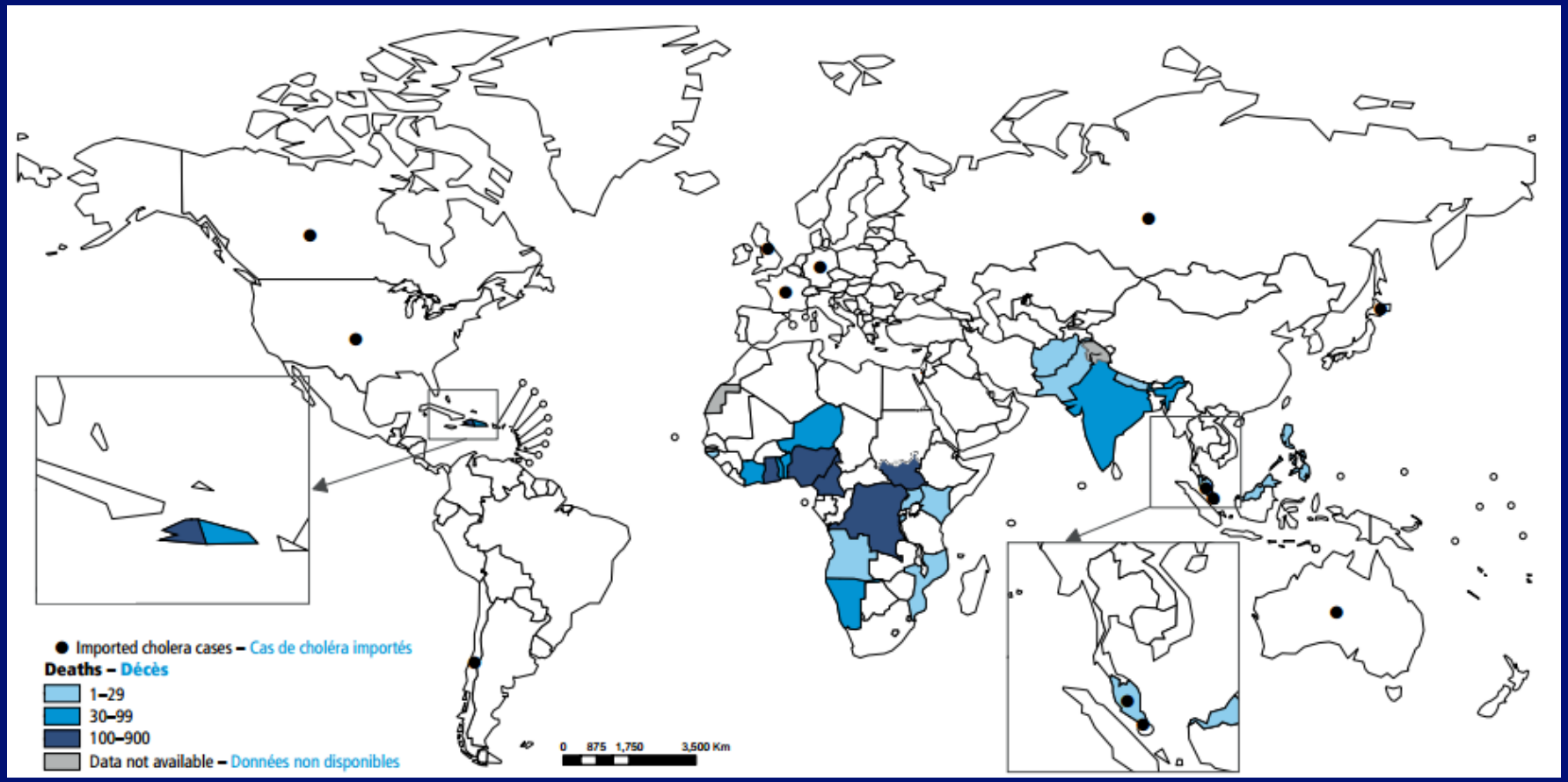
Division of Foodborne, Waterborne, and Environmental Diseases

Background

- Caused by Gram-negative, rod-shaped, toxigenic *Vibrio cholerae* O1 (>99% of global cases) or O139
- Watery diarrhea that may be severe and rapidly fatal without proper treatment
- Endemic in >50 countries; may also cause epidemics
- Estimated 3–5 million cases of illness and 100,000–130,000 deaths annually

Countries reporting cholera deaths and imported cases to the World Health Organization, 2014



World Health Organization Weekly epidemiological record. 2 Oct 2015. No. 40, 2015, 90, 517–544.
http://www.who.int/wer/2015/wer9040.pdf?ua=1

Countries reporting cholera deaths and imported cases to the World Health Organization, 2014

- **Deaths reported by 24 countries in**
  - Africa (1,882)
  - Asia (42)
  - Caribbean [Hispaniola] (307)
- **Imported cases reported by 11 countries**
  - Australia (2)
  - Canada (2)
  - Chile (1)
  - France (1)
  - Germany (1)
  - Japan (5)
  - Malaysia (33)
  - Russia (1)
  - Singapore (2)
  - United Kingdom (14)
  - United States (7)

World Health Organization Weekly epidemiological record. 2 Oct 2015. No. 40, 2015, 90, 517–544. http://www.who.int/wer/2015/wer9040.pdf?ua=1

Microbiology

- ***V. cholerae*** **classified by O-antigen structure**
- **>200 O serogroups have been identified**
- **World Health Organization defines cholera as illness caused by toxigenic O1 and O139 (because they have caused cholera epidemics)**
  - O1 biotypes: El Tor and classical
  - O1 serotypes: Inaba and Ogawa

Pathogenesis

- ***V. cholerae* colonizes small intestine and produces cholera toxin**
- **Cholera toxin**
  - The A subunit causes secretory diarrhea
  - Five identical B subunits surround A subunit and bind toxin to cell membrane receptors

Transmission

- **Easily transmitted by water and food contaminated by human feces or environmental reservoirs**
  - Grows rapidly in warm, moist, non-acidic foods
  - Does not tolerate drying, acidity, or sunlight
  - Attaches to copepods (zooplankton), which can be consumed with contaminated water or food
- **Incubation period: hours to 5 days**
- **Duration: 1 to a few days**
- **Secondary cases rare if sanitation is adequate**

Spectrum of clinical illness

- **Clinical presentation ranges from no apparent symptoms to severe hypovolemic shock (cholera gravis)**
- **Risk factors for cholera gravis include**
  - High dose exposure
  - Low gastric acidity: gastrectomy, antacid therapy
  - Blood group O (prevalence in United States ~45%)
  - Other strain and population factors

Harris JB *et al*. Blood group, immunity, and risk of infection with *Vibrio cholerae* in an area of endemicity. Infect Immun. 2005 Nov;73(11):7422-7.

http://www.redcrossblood.org/learn-about-blood/blood-facts-and-statistics

Cholera gravis

- Profuse watery diarrhea (can be ≥1 L/hour)
- “Rice-water stools” flecked with mucus and epithelial cells
- Vomiting
- Leg cramps
- Severe dehydration: loss of skin turgor, hypotension, weak pulse, altered mental status
- Rapidly fatal if untreated

Cholera in an American physician, 1971

- **8 AM:** acute onset of profuse, brown, watery diarrhea; diffuse abdominal cramps; and anorexia
- **9 AM:** oral rehydration and antibiotics started
- **11 AM:** light-headedness and nausea
- **12 PM:** blood pressure 80/60 mm Hg; pulse 116
- **12:20 PM:** persistent, severe muscle cramps in both lower legs
- **3 PM:** rice-water stool while en route to hospital
- **5 PM (at hospital):** 4 kg [8.8 lbs] weight loss since previous week
- **Day 2, 2 PM:** discharged, having passed 8,870 ml of stool and having received 10.4 liters of intravenous solution
- **4 days later:** patient returned to duty

Abrutyn E *et al*. Cholera in a vaccinated American. Immunological response to vaccination and disease. Ann Intern Med. 1971 Feb;74(2):228-31.

Diagnosis

- **Diagnosis by culture of rectal swab or stool specimen**
  - Underdiagnosis common because special transport media and culture media are needed
- **Serologic diagnosis: acute/convalescent vibriocidal titers**
  - Increase 2 weeks after exposure
  - Decrease 2 months after illness

Clinical management

- **Supportive care: oral/intravenous rehydration can reduce fatality rate to <1%**
- **Antimicrobial therapy in conjunction with hydration**
  - Recommended for severely ill patients and all hospitalized patients
  - Reduces fluid loss, duration of illness, duration of fecal carriage
- **Zinc supplementation in children reduces duration of illness and volume of diarrhea**

Immunity

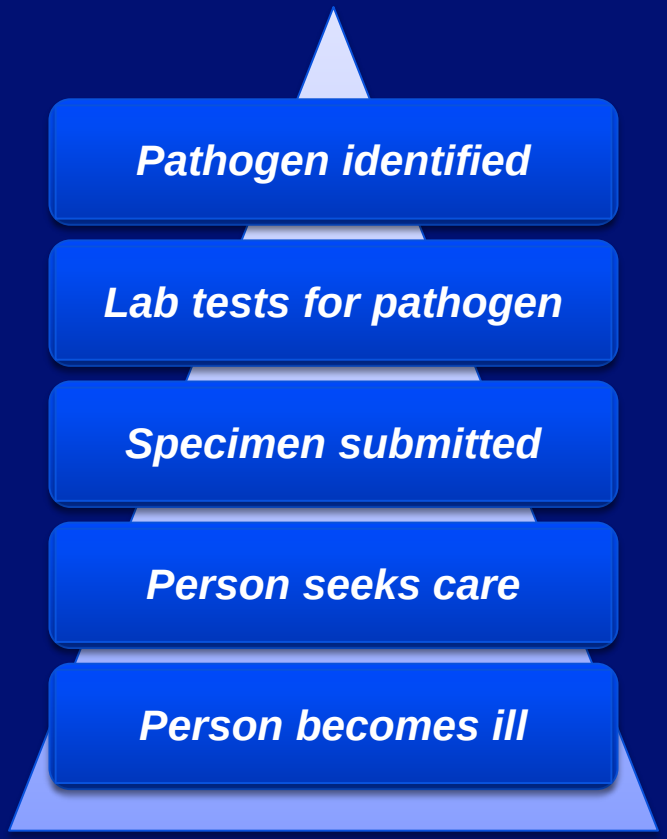
- Vibriocidal antibodies are best marker for protection against *V. cholerae* infections
- LPS-specific memory B cells may play role in mediating long term protection
- Protection against cholera is serogroup-specific (O1 or O139) but protects across biotypes (El Tor and Classical) and serotypes (Inaba and Ogawa)

Cholera in industrialized countries is mostly travel-associated

- Very rare in United States and other countries with safe water and modern sanitation
- Few domestically acquired cases in United States; many of them associated with Gulf Coast seafood consumption
- Most US cases are associated with travel to cholera-endemic countries

Cholera is underreported in the United States

- Testing for *V. cholerae* is not routine
- Some cholera illnesses in travelers are not severe and may resemble other causes of traveler's diarrhea



Selected estimates of laboratory-confirmed cholera incidence in returning travelers

Population	Incidence per 100,000 people
European and North American travelers to South America, 1991 (during cholera epidemic)	0.3
Japanese travelers to Indonesia, 1991	13
All travelers returning from developing world seeking care at GeoSentinel clinics*, 1996–2004	5.8

- **Interpretation should consider differences in surveillance methods**

*GeoSentinel clinics: clinics belonging to a worldwide surveillance network that tracks infectious diseases in returned travelers, foreign visitors, and immigrants

Wittlinger F *et al*. Risk of Cholera Among Western and Japanese Travelers. J Travel Med. 1995 Sep 1;2(3):154-158.
Freedman DO *et al*. Spectrum of disease and relation to place of exposure among ill returned travelers. N Engl J Med. 2006 Jan 12;354(2):119-30.

Selected estimates of laboratory-confirmed cholera incidence among persons traveling or living in cholera-affected areas

Population	Incidence per 100,000 people
US citizens living in Peru, 1991–1993	44 per month
US citizens providing medical services in Haiti, 2010–2011	321*
Travelers seeking care during travel to Nepal, multiple years between 1986 and 2011	0**

- **Haiti, December 2010: Cholera outbreak affected 10/14 (71%) French medical volunteers and 11/72 (15%) French military police engaged in response efforts**

* 1 of 311 respondents reported receiving a diagnosis of cholera

** 0 cholera cases diagnosed among 898 travelers seeking care for traveler's diarrhea

Taylor DN *et al*. Cholera among Americans living in Peru. Clin Infect Dis. 1996 Jun;22(6):1108-9.

Schilling KA *et al*. Diarrheal illness among US residents providing medical services in Haiti during the cholera epidemic, 2010 to 2011. J Travel Med. 2014 Jan-Feb;21(1):55-7.

Murphy H, Pandey P. Pathogens for travelers' diarrhea in Nepal and resistance patterns. Curr Infect Dis Rep. 2012 Jun;14(3):238-45.

Haus-Cheymol R *et al*. A cluster of acute diarrhea suspected to be cholera in French travelers in Haiti, December 2010. J Travel Med. 2012 May-Jun;19(3):189-91.

Cholera outbreak among passengers of a commercial airline flight from South America, 1992

- **Flight from Buenos Aires, Argentina → Lima, Peru → Los Angeles, United States**
- **Contaminated seafood salad prepared in Lima and served to passengers**
- **100/194 passengers tested had evidence of *V. cholerae* O1 infection**
  - 75 had diarrhea (median 2 days after arrival)
  - 10 patients hospitalized
  - 1 patient died (70 years of age)
  - 19 cholera patients were US citizens

Eberhart-Phillips J *et al*. An outbreak of cholera from food served on an international aircraft. Epidemiol Infect. 1996 Feb;116(1):9-13.

Cholera in the United States, 2001–2011

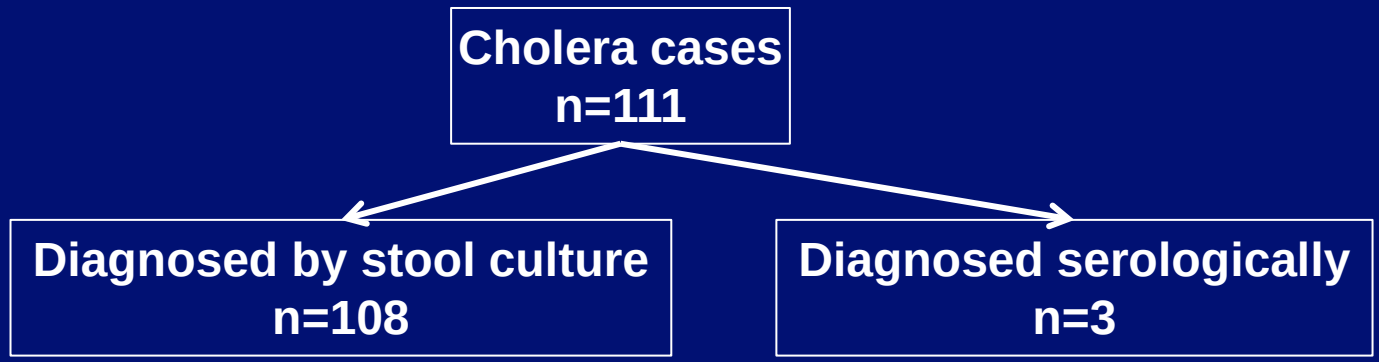
- 111 cholera cases reported in United States over 11-year period
- Epidemic cholera began in Haiti in October 2010
- 46% of cases over study period reported after Haiti epidemic began
- No secondary cases reported

Loharikar A *et al*. Cholera in the United States, 2001-2011: a reflection of patterns of global epidemiology and travel. *Epidemiol Infect*. 2015 Mar;143(4):695-703.

Cholera in the United States, 2001–2011

- **20 (18%) domestically acquired; most reported seafood consumption**
- **90 (81%) associated with international travel**
  - Visiting friends and relatives (62%)
  - Medical missions or other relief work (9%)
  - Tourism (7%)
  - Business (7%)
  - Immigration to the United States (5%)
- **74/87 (85%) travel-associated *V. cholerae* O1 cases had isolate with multidrug resistance**

Laboratory characteristics of isolates from cholera cases— United States, 2001–2011



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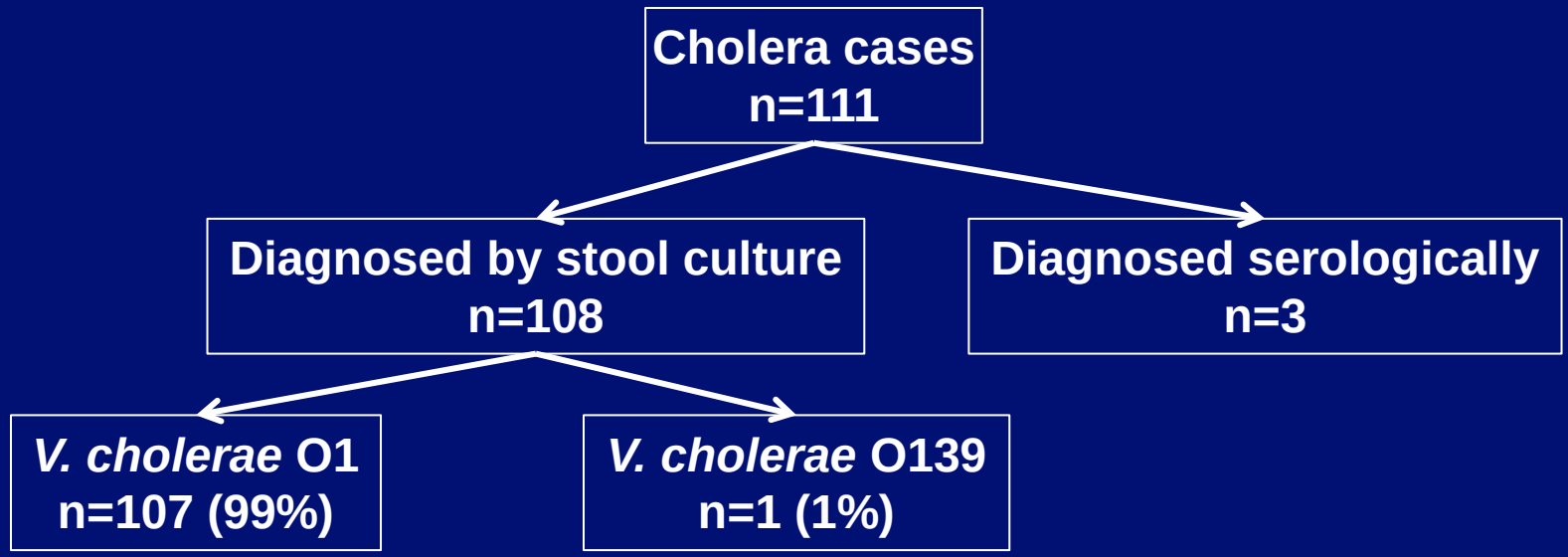

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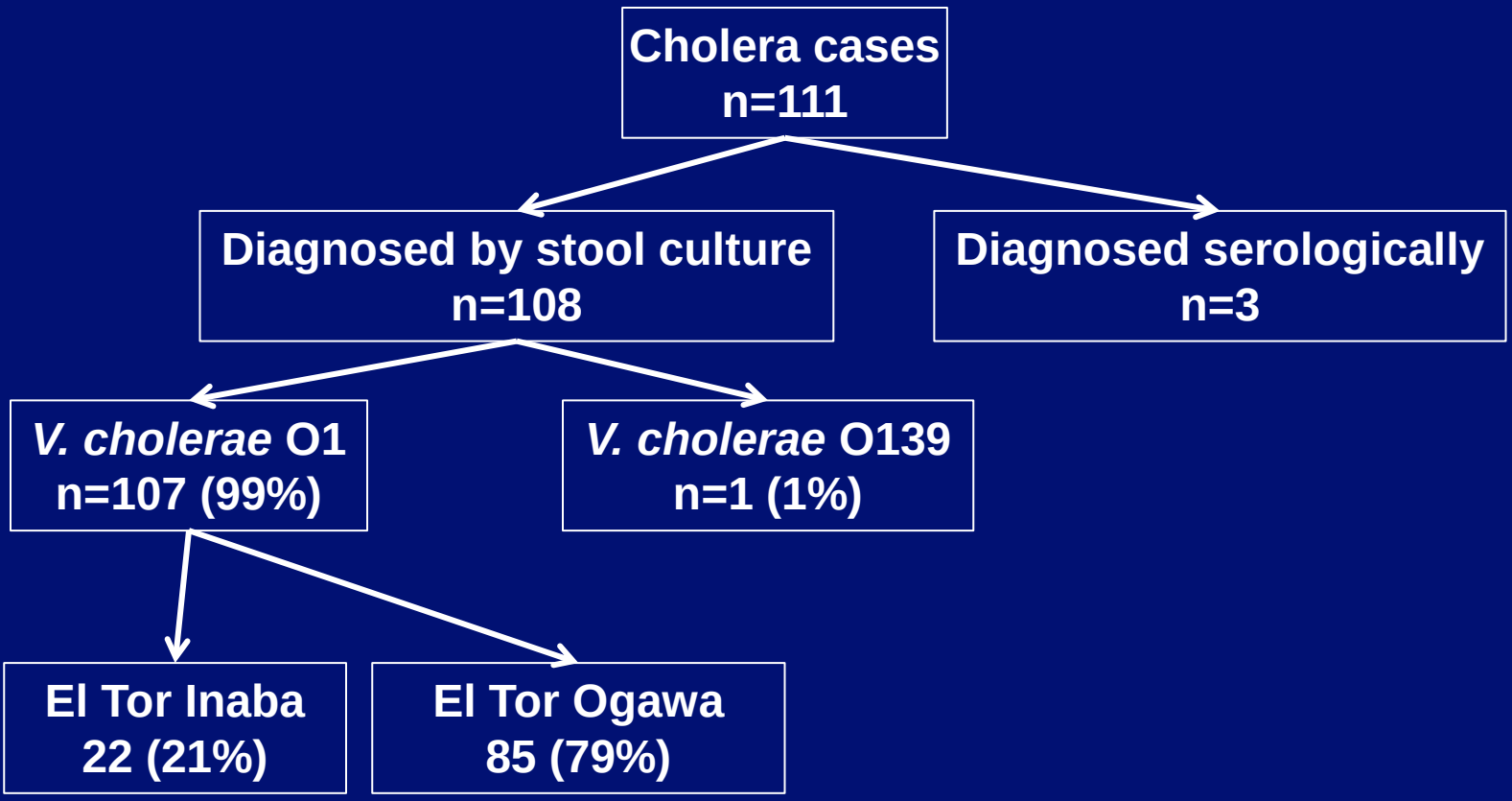

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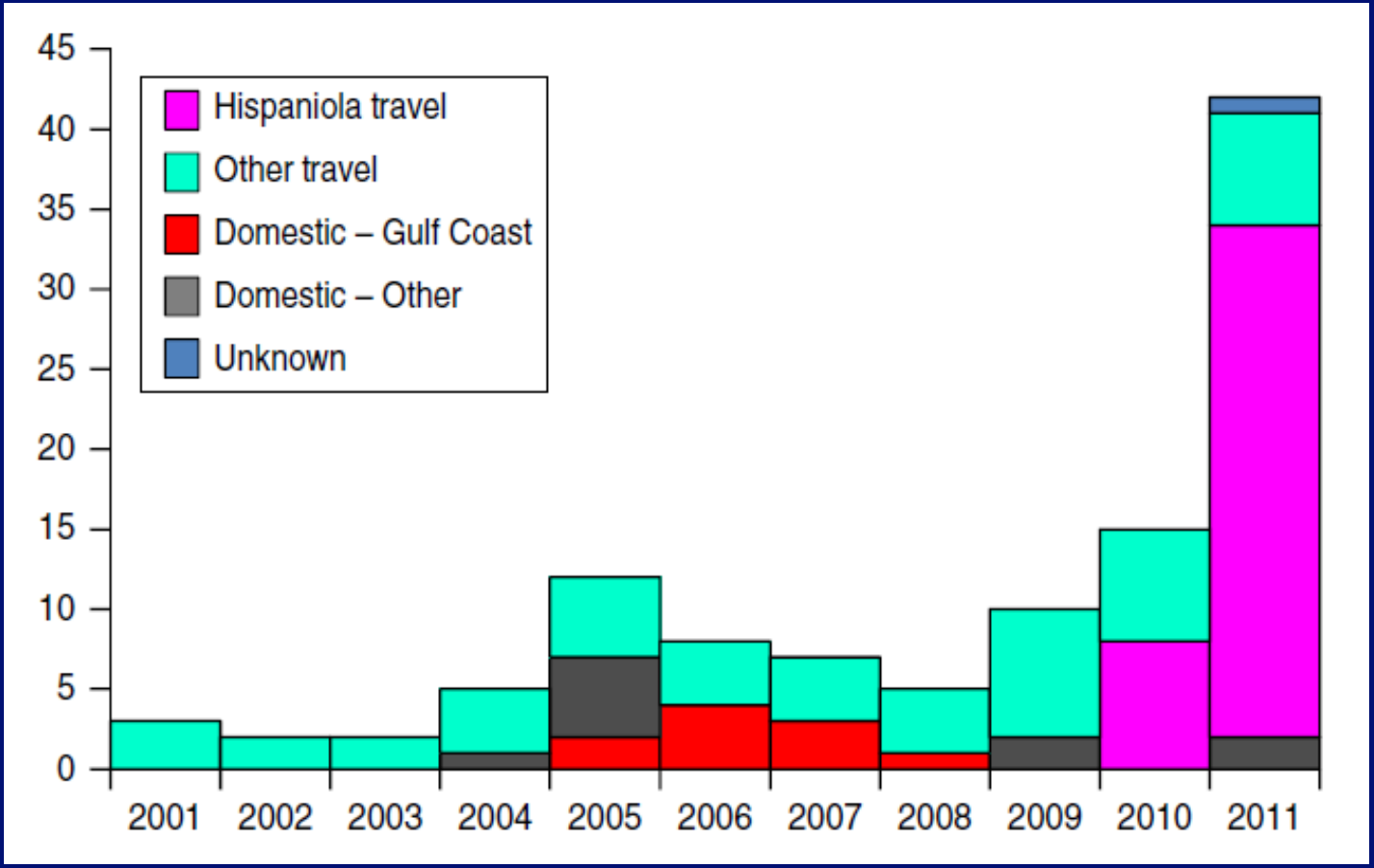
Number of cholera cases by year, and by source 2001–2011, United States (n=111)



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Cholera and Other *Vibrio* Illness Surveillance—United States, 2012–2013

- **30/32 (94%) patients with cholera reported in United States had traveled to cholera-endemic area**
  - Haiti (18), Dominican Republic (4), Other (8)
- **1 healthcare worker with no travel exposure who cared for a cholera patient in the hospital**
- **1 reported exposure in a laboratory**
- **Age 1–87 years**

http://www.cdc.gov/ncezid/dfwed/pdfs/covis-annual-report-2012-508c.pdf . Accessed October 8, 2015.
http://www.cdc.gov/ncezid/dfwed/pdfs/covis-annual-report-2013-508c.pdf . Accessed October 8, 2015.

Summary of cholera features

- Severe cholera (cholera gravis) can be rapidly fatal if untreated
- Cholera is under-reported
- Few cases are reported in the United States, although incidence increased after outbreak in Haiti began
- Most cases in United States occur in persons who have recently traveled to cholera-affected areas
- Few cases in healthcare workers and laboratory personnel providing medical services to cholera patients

Current CDC recommendations for US travelers to cholera-affected areas

- Current prevention recommendations center on safe food and water precautions and frequent handwashing
- Chemoprophylaxis not indicated
- No vaccine recommendation; no cholera vaccine licensed in United States
- WHO prequalified vaccines (Dukoral, Shanchol) are mentioned

http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/cholera. Accessed October 8, 2015

WHO recommendations for travelers to cholera-endemic areas

- **"The risk for most travelers is very low, even in countries where cholera epidemics occur, provided that simple precautions are taken. However, humanitarian relief workers in disaster areas and refugee camps may be at risk"**
- **Consider for travelers at high risk:**
  - Killed oral O1 with whole-cell with B-subunit (Dukoral)
  - Killed oral O1 and O139 (Shanchol)
- **October 2, 2015: SAGE* Working Group forming to revise WHO recommendations on oral cholera vaccines**

* Strategic Advisory Group of Experts (SAGE) on Immunization
http://www.who.int/ith/vaccines/cholera/en/. Accessed October 8, 2015.
http://www.who.int/immunization/policy/sage/call_sage_wg_ocv/en/. Accessed October 8, 2015.

Global cholera vaccines for travelers

- **No vaccine licensed in United States**
- **Shanchol (ShanthaBiotechnics, India)**
  - Licensed in India
  - 2 oral doses 2–6 weeks apart
- **Dukoral (Crucell, the Netherlands)**
  - Licensed in >60 countries, primarily as vaccine for travelers to cholera-endemic areas
  - Sweden and Canada: approved for traveler's diarrhea prevention
  - Short-term protection against enterotoxigenic *E. coli*
  - 2 oral doses ≥7 days apart; requires buffer solution
- **No country requires vaccination against cholera as condition for entry**

CVD 103-HgR: single-dose, live attenuated oral cholera vaccine under consideration for US travelers

- Recombinant *V. cholerae* O1, Classical biotype, serotype Inaba; confers protection against multiple biotypes and serotypes
- 94% of the enzymatically active A subunit of toxin gene deleted
- Gene for the antigenic, non-toxic B subunit of toxin intact
- Does not express enzymatically active cholera toxin
- Contains marker to differentiate the vaccine strain from wild-type *V. cholerae* O1

CVD 103-HgR: single-dose, live attenuated oral cholera vaccine under consideration for US travelers

- Previously licensed as Orochol/Mutacol and used in non-US countries including Switzerland, Canada, Australia
- Manufacture ceased for business reasons in 2004
- In 2009, PaxVax acquired licensure rights to redevelop CVD 103-HgR (Vaxchora) for commercial use

ACIP Cholera Vaccine Work Group

- Review evidence for use of CVD 103-HgR and evaluate according to GRADE framework
- Inform recommendations for use of CVD 103-HgR in adult travelers in anticipation of US licensure

Anticipated next steps

- February 2016: Presentation of GRADE evaluation; presentation by vaccine manufacturer
- June 2016: Presentation of working group recommendations regarding use in adult travelers

Thank you

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
Visit: www.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info